High copeptin concentrations in umbilical cord blood after vaginal delivery and birth acidosis

Wellmann, S ; Benzing, J ; Cippà, G ; Admaty, D ; Creutzfeldt, R ; Mieth, R ; Beinder, E ; Lapaire, O ; Morgenthaler, N G ; Haagen, U ; Szinnai, G ; Bührer, C ; Bucher, H U

Abstract: CONTEXT: The pituitary-secreted nonapeptide arginine-vasopressin (AVP) is unstable and therefore unsuited for diagnostic use, but its secretion can be estimated by measuring copeptin, the C-terminal portion of the AVP precursor (pro-AVP). OBJECTIVE: Our objective was to investigate perinatal factors affecting copeptin concentrations in infants at birth and at 3 d of life. DESIGN AND SETTING: We conducted a prospective cross-sectional study at a tertiary university hospital. PATIENTS: Copeptin plasma concentrations were evaluated in 177 infants at birth, including 117 paired arterial/venous umbilical cord and 102 venous blood samples obtained at 3 d of life. MAIN OUTCOME MEASURE: Copeptin concentrations were determined by a C-terminal pro-AVP luminescence immunoassay. RESULTS: Arterial umbilical cord copeptin concentrations were consistently higher than matched venous ones (median 18 vs. 10 pmol/liter, $P < 0.001$), but both values were closely related ($R(s) = 0.825$; $P < 0.001$), and both were negatively related to arterial umbilical cord pH (R(s) arterial/venous = -0.578/-0.639; $P < 0.001$). Although exceedingly high copeptin concentrations were observed after vaginal birth in umbilical cord arterial [median (5-95% range) = 1610 (85-5000) pmol/liter] and venous [793 (6-4836) pmol/liter] plasma, copeptin concentrations were low after primary cesarean section [arterial/venous = 8 (3-907)/5 (5-504) pmol/liter]. Postnatal body weight loss was associated with increased copeptin concentrations at d 3 ($R(s) = 0.438$; $P < 0.001$) and was inversely related to copeptin concentrations at birth (R(s) = -0.289 and -0.309; both $P = 0.001$). CONCLUSION: Vaginal birth is associated with a large release of copeptin that exceeds all values published so far, including those in critically ill adult patients with shock or brain injury. Thus, vaginal birth is arguably the most intense stressor in life.

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High copeptin concentrations in umbilical cord blood after vaginal delivery and birth acidosis

Short title: Copeptin at birth and in postnatal adaptation

Sven Wellmann (1), Jörg Benzing (2), Giuditta Cippà (1), Deborah Admaty (1), Ruth Creutzfeldt (1), Romaine Arlettaz Mieth (1), Ernst Beinder (3), Olav Lapaire (4), Nils G Morgenthaler (5), Ulrike Haagen (5), Gabor Szinnai (6), Christoph Bührer (7), and Hans Ulrich Bucher (1)

(1) Department of Neonatology, University Hospital Zurich, Switzerland
(2) Department of Neonatology, University Children's Hospital Basel, Switzerland
(3) Department of Obstetrics, University Hospital Zurich, Switzerland
(4) Devision of Obstetrics and Gynecology, University Hospital Basel, Switzerland
(5) Research Department, B.R.A.H.M.S AG, Hennigsdorf, Germany
(6) Pediatric Endocrinology, University Children's Hospital Basel, Switzerland
(7) Department of Neonatology, Charité University Medical Center, Berlin, Germany

Corresponding author and for reprints: Dr. Sven Wellmann, Klinik für Neonatologie, UniversitätsSpital Zurich, Frauenklinikstr. 10, CH-8091 Zurich, Switzerland
sven.wellmann@usz.ch; Tel.: +41 44 255 5340; Fax: +41 44 255 4442

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Précis: Copeptin levels in infants at birth correlate directly with the extent of birth stress and the degree of postnatal weight loss.

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Precise summary: Copeptin concentrations were higher in arterial than in venous umbilical cord plasma, both values were closely related and high in infants delivered vaginally and/or suffering from birth acidosis. High copeptin at birth was linked with decreased postnatal dehydration. The extent of postnatal dehydration correlated directly with copeptin at day 3.

Key terms: Copeptin; vasopressin; postnatal adaptation; umbilical cord blood

Abbreviations:

AVP	Arginine-vasopressin
CT-proAVP	C-terminal portion of the AVP precursor
ADH	Antidiuretic hormone
LIA	Luminescence-immunoassay
NSE	Neuron-specific enolase

Abstract

CONTEXT: The pituitary-secreted nonapeptide Arginine-Vasopressin (AVP) is unstable and therefore unsuited for diagnostic use but its secretion can be estimated by measuring copeptin, the C-terminal portion of the AVP precursor (CT-proAVP).

OBJECTIVE: To investigate perinatal factors affecting copeptin concentrations in infants at birth and at 3 days of life.

DESIGN and SETTING: We conducted a prospective cross-sectional study at a tertiary university hospital.

PATIENTS: Copeptin plasma concentrations were evaluated in 177 infants at birth, including 117 paired arterial/venous umbilical cord and 102 venous blood samples obtained at 3 days of life.

MAIN OUTCOME MEASURE: Copeptin concentrations, determined by a CT-proAVP-Luminescence-immunoassay.

RESULTS: Arterial umbilical cord copeptin concentrations were consistently higher than matched venous ones (M 18 vs. 10 pmol/l, $p<0.001$) but both values were closely related ($Rs=0.825$, $p<0.001$), and both were negatively related with arterial umbilical cord pH (Rs arterial/venous = -0.578/-0.639, $p<0.001$). While exceedingly high copeptin concentrations were observed after vaginal birth in umbilical cord arterial (M [5-95% range]: 1610 [85-5000] pmol/L) and venous plasma (793 [6-4836] pmol/L), copeptin concentrations were low after primary caesarean section (arterial/venous 8 [3-907]/5 [5-504] pmol/L). Postnatal body weight loss was associated with increased copeptin concentrations at day 3 ($Rs=0.438$, $p<0.001$) and was inversely related to copeptin concentrations at birth ($Rs=-0.289$ and -0.309, both $p=0.001$).

CONCLUSION: Vaginal birth is associated with a large release of copeptin that exceeds all values published so far, including those in critically ill adult patients with shock or brain injury. Thus, vaginal birth is arguably the most intense stressor in life.

Introduction

Crucial integration of a variety of neural and endocrine events is a prerequisite for the successful adaptation to extrauterine life. Parturition evokes a dramatic surge in stress hormones facilitating the transition of the newborn to air breathing, cardiovascular adaptation, thermogenesis, glucose and water homeostasis.

The nonapeptide arginine-vasopressin (AVP), also known as antidiuretic hormone (ADH), is one of these stress hormones. AVP was first reported to be increased in cord blood more than 30 years ago (1)· (2). However, the measurement of AVP levels is laborious and for clinical use unsuited because of its instability and short half-life. AVP derives from a larger precursor peptide (provasopressin) together with two other peptides, neurophysin II and copeptin. Copeptin is released in an equimolar ratio to AVP, circulates in plasma without physiologic activity, is highly stable especially after Ca^{2+} chelation by EDTA, and easy to measure (3).

This study aimed to evaluate copeptin concentrations in paired samples of arterial and venous cord blood of newborn infants as well as in venous blood collected 3 days after birth.

Subjects and methods

The study was carried out between July and September 2009. After obtaining written informed consent, pregnant women presenting for delivery at the University Hospital Zurich, Switzerland, were included. The study was approved by the institutional review board.

Of the 177 infants studied, 141 (80%) were term (37-41 completed weeks of gestational age), 21 were near-term (35 or 36 weeks), and 15 had a gestational age of 32-34 weeks. Twenty-four (13.6%) infants were twins and 3 (1.7%) triplets. Sixty-two of the 177 infants were delivered vaginally (35%), including 17 (9.6%) requiring instrumental support; 115 (65%) were delivered by caesarean section, including 40 cases of secondary caesarean section due to acute fetal or maternal distress. The percentage of deliveries by caesarean section was significantly higher in preterm infants (31 of 36, 86%) than in term infants (83 of 141, 59%, p=0.003).

Blood samples were drawn from 143 umbilical veins at the time of delivery with additional 117 paired samples from umbilical artery and additional 68 paired samples from venous blood at postnatal day 3. Auxiliary blood samples were taken at postnatal day 3 from 34 children.

Details of pregnancy (presence or absence of preeclampsia, diabetes, infection, preterm labour, or administration of betamethasone for fetal lung maturation), delivery (umbilical artery pH, base deficit, and hematocrit; amount of maternal blood loss) and the infants' birth characteristics (gestational age, birth weight, Apgar scores at 5 and 10 min) were collected from the charts. The data on infants' health after birth, whether the infants were exclusively breast fed, additionally fed with formula, or given intravenous fluid, and the daily weight control were recorded by the staff on the maternity or neonatology ward, respectively. Characteristics of mothers and infants are summarized in Table 1.

Blood samples were collected immediately after birth by puncture of the umbilical cord artery and vein, and at 72 hours (± 8 hours, postnatal day 3) after birth by puncture of a vein from the back of the hand. After collecting blood in EDTA tubes, samples were stored at 4°C not exceeding 4 hours until centrifugation was performed and plasma was transferred in a new EDTA tube and subsequently frozen at -28°C. Measurement was done in a single batch with a research sandwich immunoluminometric assay (B.R.A.H.M.S CT-proAVP LIA, B.R.A.H.M.S AG, Hennigsdorf, Germany) as described elsewhere (3), except that the capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137-144 (GRAGAL) of proAVP.

Statistical analyses were made using PASW 18.0 (SPSS inc., Chicago, Ill.) with strictly non-parametric tests (Spearman's rank order correlation, Mann-Whitney U test, Kruskal-Wallis, or Fisher's exact test).

Results

Paired umbilical cord arterial and venous plasma copeptin concentrations were closely related (n=117, Rs=0.825, $p<0.001$). Copeptin concentrations were consistently higher in arterial than in venous samples (M 18 vs 10 pmol/L, $p<0.001$). Copeptin concentrations measured at 3 days of life (n=102, M [5-95% range] 14.0 [5.5-56.6] pmol/L) were significantly ($p<0.001$) lower than copeptin

concentrations in either umbilical cord arterial or venous plasma. There was neither a correlation of copeptin concentrations in paired samples of arterial umbilical cord plasma and day 3 venous plasma ($n=54$, $Rs=-0.061$, $p=0.664$) nor in paired samples of venous umbilical cord plasma and day 3 venous plasma ($n=68$, $Rs=-0.133$, $p=0.281$).

Analyzing copeptin concentrations in respect to clinical dates revealed a significant ($p<0.001$) inverse correlation of copeptin concentrations in both arterial umbilical cord plasma and venous umbilical cord plasma with umbilical artery pH ($Rs=-0.639$, $Rs=-0.578$, respectively) and umbilical artery base excess ($Rs=-0.645$, $Rs=-0.638$, respectively), as shown in Fig. 1. Apgar scores at 5 and 10 min of life, hematocrit in umbilical cord blood as well as mothers' blood loss during delivery did not correlate with copeptin concentrations in any plasma samples, neither arterial and venous umbilical cord plasma nor plasma samples drawn at day 3.

The mode of delivery affected copeptin concentrations in arterial and venous umbilical cord plasma very strongly (both $p<0.001$), see Fig. 1, but had no impact on copeptin concentrations in day 3 venous plasma. The distributions of copeptin concentrations in arterial and venous umbilical cord plasma in respect to the various delivery modes are summarized in Table 2.

Gestational age was found to be directly related with copeptin concentrations in arterial and venous umbilical cord plasma ($Rs=0.377$, $Rs=0.416$, both $p<0.001$, respectively) but not with copeptin concentrations in day 3 venous plasma. However, birth weight depicted only a weak correlation to copeptin concentrations in venous umbilical cord plasma ($Rs=0.183$, $p=0.029$) but not with copeptin concentrations in either arterial umbilical cord plasma or day 3 venous plasma. This finding of lower copeptin concentrations in umbilical cord blood of infants born preterm or with low birth weight was mainly attributed to the fact that the percentage of deliveries by caesarean section was significantly higher in preterm infants (31 of 36, 86%) than in term infants (83 of 141, 59%, $p=0.003$).

The maximal weight loss in postnatal adaptation occurred between day 2 and 5, on average at day 3. Intravenous fluid was administered in 8 infants, all of whom weighed below 1800 g at birth and therefore received intravenous fluid following institutional guidelines. Only 40 infants of the study

population were exclusively breast fed, 62 received some additional hydrolyzed starch solution, and 67 received formula milk with or without mother's milk.

There was an inverse relation between maximal weight loss and copeptin concentrations in arterial as well as in venous umbilical cord plasma (Rs=-0.309, Rs=-0.289, both p=0.001, respectively) indicating increased postnatal weight loss in infants with low copeptin concentrations at birth. Then we compared copeptin concentrations in venous umbilical cord plasma in all infants subdivided in groups with mild (2-5%, n=33), moderate (6-7%, n=51), and severe maximal postnatal weight loss (8-12%, n=53). Copeptin concentrations at birth were significant higher in infants with mild as compared to moderate or severe maximal postnatal weight loss (p=0.017 and p<0.0001, respectively, Fig. 2A).

Maximal weight loss correlated directly with copeptin concentrations in venous plasma drawn at 3 days of life (Rs=0.438, p<0.001) but neither with sodium concentrations, hematocrit, or bilirubin at day 3. All infants with copeptin values from day 3 were subdivided in groups with mild (n=29), moderate (n=36), and severe maximal postnatal weight loss (n=37). Copeptin concentrations at day 3 were significant higher infants belonging to the group with severe as compared to mild or moderate maximal weight loss (p<0.0001 and p=0.011, respectively, Fig. 2B.

There was neither a relation between maximal weight loss and gestational age at birth nor between maximal weight loss and birth weight.

Discussion

Until now, copeptin had been studied exclusively in adults. These studies were done with respect to changes in plasma osmolality, in settings of mild to life-threatening physical stress, and in various diseases. Normal copeptin concentrations in healthy adults were consistently reported to be about 5 pmol/L, as reviewed by Morgenthaler NG et al. (4). Water deprivation has been shown to increase copeptin concentrations 4-fold (M 19.9 [mean ± SD 4.8] pmol/L) (5) and severe stress e.g. extubation of surgical patients was found to result in a 10-fold increase (M 67.5 [interquartile range 37.8-110] pmol/L) (6). The most pronounced surges in copeptin hitherto described were in patients suffering from shock, either septic (M 375 [range 59-1572] pmol/L) (7) or hemorrhagic (M 269 [range 241-456]

pmol/L) (8). These 20-fold increased copeptin concentrations in adults suffering from life threatening events are still far below the copeptin concentrations we measured in healthy, naturally delivered infants. Determination of copeptin concentrations in all these studies investigating adults was performed by the same CT-proAVP LIA as applied here, allowing for a direct comparison. Thus, vaginal delivery provokes a unique surge in copeptin plasma concentration (Figure 1) incommensurable with all reported changes in copeptin concentrations in adult patients.

Hypoxia has been described to augment a strong AVP release within short time in various animal models (9-13) and similarly, perinatal asphyxia in humans has been found to trigger a decisive AVP response (14-15). As also normal vaginal delivery in humans has been shown to trigger AVP release (1-2), some investigators have come up with the hypothesis that fetal AVP release may effectively reduce placental blood flow during uterine contraction. This could contribute to acute fetal stress and hypoxia even during normal labour (16-18). However, our finding that copeptin concentrations in umbilical cord plasma are orders of magnitude (on average 500 times) higher in infants delivered vaginally as compared to those delivered by elective caesarean section indicate that vaginal birth is the largest stressor for the body found so far, e.g., larger than brain trauma, ischemic stroke or severe shock in adults (19-20, 7-8).

Copeptin concentrations in arterial umbilical cord plasma were found to be on average 1.8-fold above those in paired venous umbilical cord plasma samples. As copeptin appears to be too large (39 amino acid glycopeptide) to cross the placental barrier, this observation leads to two hypotheses: First, measured copeptin levels in cord blood are of fetal origin and second, some circulating copeptin is captured during the placental passage. Copeptin is thought to be without physiological function, and therefore the placental clearance is somewhat surprising.

In our study most newborns were born at term but 36 (20%) were born between 32 and 36 completed weeks of gestation. Although there was a significant positive and moderate correlation of copeptin levels in arterial and venous cord blood with gestational age, there was no consistent relationship with birth weight. A closer view on this finding reveals that the high percentage of caesarean sections within the group of preterm infants (86%) accounted for their overall low copeptin levels. After adjusting for vaginal delivery and secondary caesarean section, the difference between term and

preterm infants disappeared. This is in line with previous findings investigating AVP (16, 21). One important limitation of our analysis is the small group of premature infants included, and there were no infants below 32 weeks gestational age which represent the most vulnerable group of patients in neonatal intensive care units.

AVP orchestrates a magnitude of actions covering well understood mechanisms including water retention and maintenance of blood pressure but also recently discovered roles in social behaviour (22). Thus, it is intriguing to assume that AVP is involved in postnatal physical and behavioural adaptation (e.g. bonding). Reports linking elevated AVP at birth with delayed voiding (23-24) are in support of the inverse relation of high copeptin in umbilical cord blood and minor postnatal weight loss we found in this study (Figure 2A). This may offer an explanation why infants born by caesarean section are prone to dehydration more frequently then infants delivered vaginally (25). Increased rates of breathing disorders after caesarean delivery are common (26-27), and it is tempting to speculate that low AVP after caesarean delivery is involved in compromised postnatal pulmonary adaptation. In contrast to peripheral vasculature, AVP leads to vasodilatation of pulmonary vasculature under hypoxic conditions through AVP-receptor-mediated endothelial release of NO (28-29). In addition, type II pneumocytes express AVP-receptors and have been shown to secrete surfactant when exposed to AVP (30-31). Thus, physiologic hypoxia during vaginal birth causing a robust AVP release may prepare infants for successful postnatal adaptation, whereas infants delivered by primary caesarean section (that is before the onset of labour) have no relevant AVP release and are thus less well prepared to resume respiratory oxygenation.

Even exceedingly high copeptin concentrations at birth returned to near-normal values at day 3 of life, there was no correlation between concentrations at both time points. This is in agreement with data from AVP analyses (16, 21, 32-33) and from copeptin analyses in adults with acute myocardial infarction (34). Already 24 hours after pain onset copeptin concentrations normalized in the majority of patients. Moreover, the inverse correlation of copeptin concentrations at day 3 and dehydration as indicated by the infants' weight loss implicates an intact osmotic AVP regulation (Figure 2B). Copeptin concentrations at day 3 were in about the same range as documented for adults during

adaptation to dehydration (5). Thus, we conclude that after releasing AVP at birth, there are neither unusual low copeptin concentrations followed nor a hampered osmotic AVP regulation.

While an increased AVP secretion at the time of birth appears to be beneficial with respect to lung function and water retention, the magnitude of the surge after normal vaginal delivery is surprising. Several hypotheses may be invoked: First, newborns might require disproportionately high AVP concentrations because of low receptor expression or receptor affinity in target tissues. Second, AVP has a pivotal role in adaptation after birth, warranting the effort. Third, AVP is released in high concentrations for binding to AVP-receptor expressing neurons, pituitary gland cells involved in ACTH release, and for oxytocin-receptor activation linked to bonding (22). There is indeed a fast-growing wealth of data uncovering evolutionary conserved function of vasopressin in modulating complex social behaviour and cognition.

Recent data have revealed copeptin as a novel, independent prognostic marker in adult patients with ischemic stroke (20) and with severe injury following brain trauma in adults (19). In these settings, copeptin was shown to be superior to various markers such as protein S-100B and neuron-specific enolase (NSE) in predicting severity level and outcome (20). Severe perinatal asphyxia damages brain in a manner similar to ischemic stroke resulting in hypoxic-ischemic encephalopathia, and neonatologists are looking for novel independent prognostic markers to guide clinical decision making with respect of applying therapeutic hypothermia and counselling parents. Further studies may explore whether extremely high copeptin concentrations at birth or kinetic in changes of copeptin concentrations after birth may herald poor outcome.

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1

Table 1. Selected characteristics of mothers and their infants

	venous plasma umbilical cord (n = 143)	arterial plasma umbilical cord (n= 117)	venous plasma day 3 (n= 102)
Characteristics	n (%)	n (%)	n (%)
Infant sex			
Male	78 (55)	69 (59)	60 (59)
Infant birth weight (g)			
< 2000	11 (8)	6 (5)	8 (8)
2000 - 3000	47 (32)	38 (31)	26 (26)
3001 - 4000	77 (54)	66 (56)	61 (61)
> 4000	8 (6)	7 (6)	7 (7)
Infant gestational age at birth (completed weeks)			
preterm 32 - 37	32 (22)	26 (22)	20 (20)
term 37 - 41	111 (78)	91 (78)	82 (80)
Mode of delivery			
Caesarean section primary	74 (52)	63 (54)	42 (42)
Caesarean section secondary	26 (18)	23 (20)	21 (21)
Spontaneous vaginal	30 (21)	23 (20)	28 (28)
Instrumental vaginal	13 (9)	8 (7)	11 (11)

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Table 2. Copeptin intervals in arterial (a) and venous (v) umbilical cord plasma

Mode of delivery	n a / v	Median Copeptin pmol/L a / v	95% reference interval, pmol/L a / v	P[a] a / v
Caesarean primary	63 / 73	8 / 5	3-907 / 5-504	
Caesarean secondary	23 / 27	14 / 11	4-2240 / 2-2260	< 0.01 / < 0.01
Vaginal spontaneous	23 / 30	1610 / 634	82-5000 / 6-5000	< 0.001 / < 0.001
Vaginal instrumental	8 / 13	1786 / 1324	1786-5000 / 90-4900	< 0.001 / < 0.001

[a] Significance between caesarean primary and with each other mode of delivery

2

3

Figure 1. Association of copeptin concentrations with pH in arterial umbilical cord samples.

According to the delivery mode dots are marked for vaginal spontaneous (♦) and instrumental (■), caesarean primary (Δ) and secondary (○).

Figure 2A. Correlation of copeptin in venous umbilical cord plasma with maximal postnatal weight loss.

Maximal postnatal weight loss is grouped in mild (2-5%, n=33), moderate (6-7%, n=51), and severe loss (8-12%, n=53). Data are presented as box (interquartile range) and whisker (5-95 % range) plots. Significant statistical differences were noted between the following groups: mild vs moderate p=0.017 and mild vs severe p<0.0001. No significant difference was noted between moderate vs severe, p=0.27.

Figure 2B. Correlation of copeptin in venous plasma at day 3 with maximal postnatal weight loss.

Maximal postnatal weight loss is grouped in mild (2-5%, n=29), moderate (6-7%, n=36), and severe loss (8-12%, n=37). Data are presented as box (interquartile range) and whisker (5-95 % range) plots. Significant statistical differences were noted between the following groups: mild vs moderate p=0.011 and mild vs severe p<0.0001. No significant difference was noted between moderate vs severe, p=0.054.

Fig. 1.

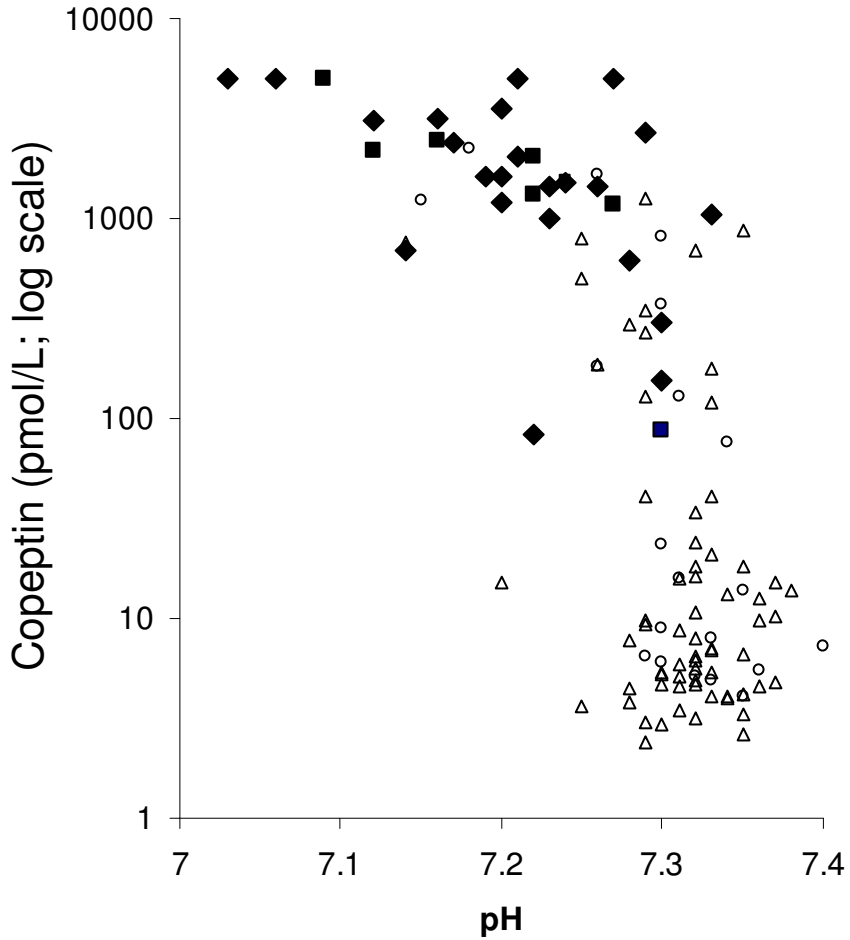


Fig. 2A

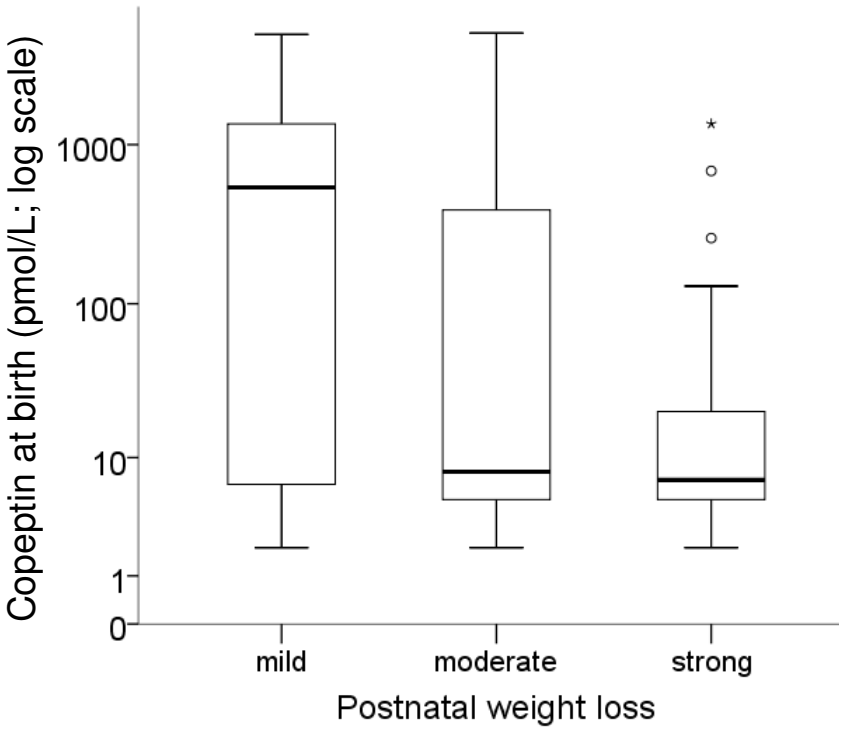
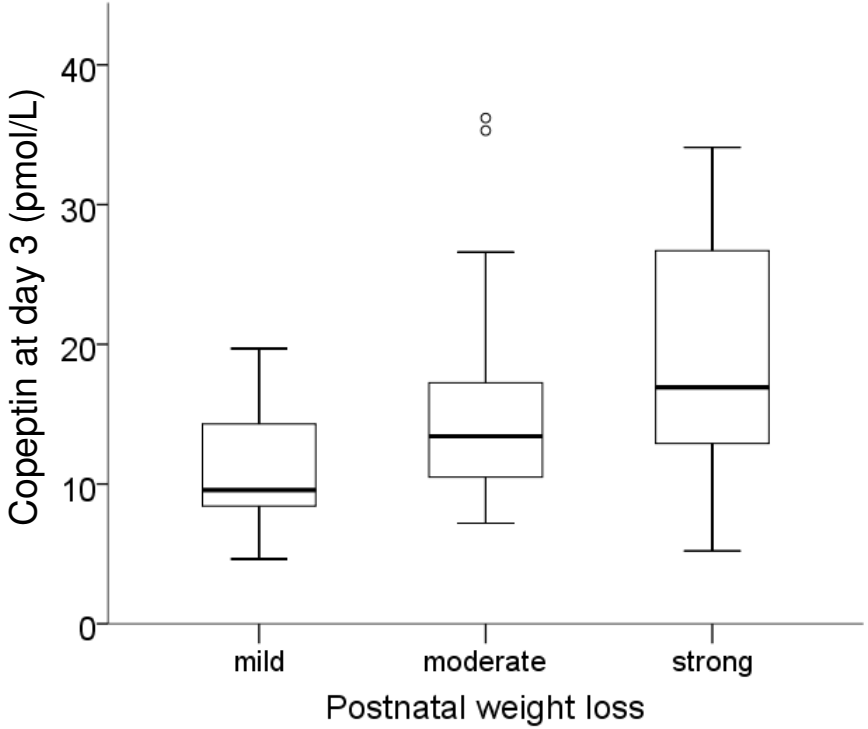

Copeptin at birth (pmol/L; log scale)
1000
100
10
1
0
mild
moderate
strong
Postnatal weight loss

Fig. 2B


Copeptin at day 3 (pmol/L)
40
30
20
10
0
mild
moderate
strong
Postnatal weight loss